



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(51) International Patent Classification<sup>3</sup> :</b><br><b>A61K 31/40, 31/195</b>   | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 83/ 00085</b><br><b>(43) International Publication Date:</b> 20 January 1983 (20.01.83)  |
| <b>(21) International Application Number:</b> PCT/US82/00742<br><b>(22) International Filing Date:</b> 28 May 1982 (28.05.82)<br><b>(31) Priority Application Number:</b> 278,914<br><b>(32) Priority Date:</b> 29 June 1981 (29.06.81)<br><b>(33) Priority Country:</b> US<br><br><b>(71) Applicant:</b> BAXTER TRAVENOL LABORATORIES, INC. [US/US]; One Baxter Parkway, Deerfield, IL 60015 (US).<br><b>(72) Inventors:</b> MADSEN, David, C. ; 600 Ardmore Terrace, Libertyville, IL 60048 (US). TUCKER, Hugh, N. ; 405 North Wabash, River Plaza No. 4210, Chicago, IL 60611 (US).<br><b>(74) Agents:</b> HENSLEY, Max, D. et al.; One Baxter Parkway, Deerfield, IL 60015 (US). |           | <b>(81) Designated States:</b> BE (European patent), DE (European patent), FR (European patent), GB (European patent), SE (European patent).<br><br><b>Published</b><br><i>With international search report.</i> |
| <b>(54) Title:</b> NUTRITIONAL COMPOSITION FOR MANAGEMENT OF HEPATIC FAILURE<br><br><b>(57) Abstract</b><br><br>Nutritional compositions for management of hepatic failure are improved by eliminating certain ammonotelic amino acids and reducing the proportion of essential ammonotelic amino acids. A composition is provided which is optimized for nutritional therapy and suppression of hyperammonemia.   |           |  |

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NUTRITIONAL COMPOSITION FOR MANAGEMENT OF HEPATIC FAILUREBackground of the Invention

This invention relates to compositions and methods for nutritional management of hepatic (liver) failure. In particular  
5 the invention is directed at novel amino acid compositions designed to meet the altered metabolic needs of patients suffering from hepatic failure and the attendant derangements of normal amino acid metabolism characterized by this clinical condition.

10 Hepatic failure has numerous potential causes. Included among these causes are traumatic injuries to the organ and metabolic causes of a chronic (e.g., alcoholism) or acute nature (e.g., hepatitis, sepsis).

Of the numerous functions performed by the liver, one in  
15 particular has importance as the subject of the invention described below. The liver is the site of detoxification of numerous substances, in particular those nitrogenous wastes associated with protein metabolism. Especially important is the toxic by-product, ammonia ( $\text{NH}_3$ ). The liver normally will  
20 detoxify ammonia by forming the nitrogen-containing substance urea (ureagenesis), which is then excreted via the kidneys.



When the liver is in various degrees of failure its ability to detoxify ammonia can become compromised. As a result ammonia can accumulate in the blood (hyperammonemia). It is a widely accepted belief among clinicians and researchers that hyperammonemia is dangerous, since ammonia is believed to be extremely toxic to the brain. A potential result of hyperammonemia is the onset or deepening of coma. When such coma is associated with hepatic failure it is termed "hepatic coma" or "hepatic encephalopathy".

10        Although the exact or immediate cause(s) of hepatic coma are not known with certainty, it is widely believed that ammonia can be a contributory factor. This is reflected in the fact that some of the non-nutritional therapeutic modalities employed in the clinical management of hepatic failure include treatments which  
15        have as their goal the reduction or elimination of ammonia input into the patient. Specifically, administration of the antibiotic, neomycin, and the synthetic carbohydrate, lactulose, are directed at reducing the production of ammonia by intestinal bacteria. It is known that the intestinal bacteria are the source of a substantial  
20        amount of ammonia, which reaches the blood-stream by intestinal absorption. Neomycin and lactulose are administered to reduce or eliminate this source of ammonia.

Current therapies for hepatic failure, with or without the complication of coma, are not generally nutritional in nature.



However, nutritional compositions which are disclosed to be tailored for hepatic failure are known. For example, see Ghadimi, U.S. Patent 3,832,405, Fischer et al, U.S. Patent 3,950,529 and West German Offenlegungsschrift 26 36 828.

5       It is known that certain amino acids (the L-forms of threonine, serine, tryptophan, glutamine, histidine, and glycine, hereafter termed "ammonotelic" amino acids) are catabolized by the body with the release of ammonia.

10       It is an object of this invention to supply an amino acid composition which will reduce the ammonia produced endogenously (by the body, rather than by bacterial flora) by reducing the proportion of ammonotelic amino acids present in the nutritional source.

15       It is another object to ameliorate the hyperammonemia which accompanies hepatic dysfunction, thereby reducing the likelihood of a lapse into hepatic coma or a deepening of the comatose state.

      It is an additional object to provide adequate nutrition to the hepatic diseased patient without compromising the foregoing two objects.

20       These and other objects will become apparent from the specification as a whole.



Summary of the Invention

We have discovered that the proportion of ammonotelic amino acids to other essential and nonessential amino acids must be carefully balanced. We believe that this proportion is critical to the successful therapy of the hepatic failure patient. Sufficient essential ammonotelic amino acids must be present to provide the required nutrients, but an excess of ammonotelic amino acids will exacerbate the clinical syndromes associated with liver disease, in particular hyperammonemia. Thus it is important that the proportion of ammonotelic amino acids not be reduced to a level at which nutrition is compromised, but that the level be sufficiently low as to not unnecessarily contribute to hyperammonemia. This is most readily accomplished by severely reducing or by eliminating L-serine, L-glycine and L-glutamine from mixtures of essential and nonessential amino acids to be used for nutritional support of liver diseased patients. The essential or semi-essential ammonotelic amino acids histidine, threonine and tryptophan are reduced to the lowest proportion compatible with effective nutritional support. The proportion of ammonotelic amino acids meeting these requirements has been found to be about from 8 to 16 mole percent of the total amino acid composition.



Detailed Description of the Invention

The compositions of this invention will contain the essential amino acids L-leucine, L-isoleucine, L-valine, L-lysine, L-threonine, L-methionine, L-phenylalanine and L-tryptophan. They may also contain the nonessential amino acids L-tyrosine, L-arginine, L-proline, L-alanine and glycine. L-histidine is considered semi-essential, and in fact may be essential for neonates. For the purposes of nutrition in liver disease and this application, histidine will be denominated an essential amino acid.

10 L-serine and L-glutamine are the ammonotelic amino acids which are most readily absent from the compositions of this invention, even though serine has heretofore been included as a required amino acid in certain prior art nutritional amino acid compositions for liver disease, e.g., those of Fisher et al, U.S. Patent 3,950,529.

15 Glycine is generally reduced to a low proportion of the total amino acids, ordinarily less than about 8 mole % and preferably about from 2 to 6 mole %. Glycine may be entirely absent from the compositions of this invention, but this is not preferred.

20 The essential ammonotelic amino acids histidine, threonine, and tryptophan are present in a proportion of about from 6 to 16 mole %, ordinarily about from 6 to 10 mole % and preferably about 8 mole %. They are not entirely eliminated from the composition as this would be incompatible with the balanced nutritional objectives of the compositions described herein.



A typical composition of this invention will contain amino acids in the following proportions:

|    | <u>Amino Acids</u> | <u>Mole Percent<br/>about from</u> |
|----|--------------------|------------------------------------|
| 5  | L-leucine          | 19.4 to 19.8                       |
|    | L-isoleucine       | 16.2 to 16.4                       |
|    | L-valine           | 14.5 to 14.8                       |
|    | L-lysine           | 10.2 to 10.3                       |
|    | L-methionine       | 1.1 to 1.2                         |
| 10 | L-phenylalanine    | 0.7 to 0.9                         |
|    | L-threonine        | 2.3 to 3.9                         |
|    | L-tryptophan       | 0.5 to 0.7                         |
|    | L-histidine        | 2.7 to 2.8                         |
|    | L-arginine         | 8.5 to 8.7                         |
| 15 | L-proline          | 8.1 to 8.3                         |
|    | glycine            | 5.6 to 5.8                         |
|    | L-alanine          | 8.1 to 8.3                         |



The relative proportions of the amino acids in the above schedule may vary by as much as about 15% of the mole percent ranges given, although in the most satisfactory composition the ranges will vary by no more than about 5%.

- 5        The ratio of essential amino acids to nonessential amino acids by weight should range about from 5:1 to 1:1. The essential amino acids should compromise about from 60 to 75% by weight of the total amino acids in the composition.

- 10       The aromatic amino acids L-phenylalanine, L-tyrosine and L-tryptophan are ordinarily present at less than about 8 mole %, preferably less than 3 mole % and optimally about from 1 to 3 mole %.

- 15       The branched chain amino acids L-leucine, L-isoleucine and L-valine are present in a total of about from 40 - 55% of the composition by weight, and preferably about 50% by weight.

Cysteine is not included in the compositions of this invention since it has been found, contrary to the teachings of Ghadami (U.S. Patent 3,832,465), that the sulfur requirements of hepatic-diseased patients may be met by supplying L-methionine.

- 20       Whether the amino acid composition is administered parenterally or enterally will depend upon the clinical condition of the patient. If the gastrointestinal tract is sound the preferred administration route is enteral. Severely comatose patients will generally be fed parenterally. In non-comatose patients the composition may be  
25       administered as a supplement to normal oral nutrition. The suitable mode of administration will be within the skill of the ordinary artisan.



The composition may be supplemented with other nutrients such as vitamins, minerals, and biologically available, assimilable carbohydrates and fats. Supplementation may occur concomitant with administration by premixing the additional nutrients with the amino acids and then administering, or by simultaneously supplying the  
5 nutrients by a separate administration route.

Parenteral compositions will ordinarily contain monosaccharides such as dextrose at typical infusion concentrations, e.g., about from 10 to 40 percent by weight. Other carbohydrates such as oligosaccharides will be satisfactory. The solutions will be sterile  
10 and may contain stabilizers such as malate or sodium bisulfite. The concentration of amino acids in solutions for parenteral administration may range about from 1 to 10 grams/dl, and preferably is about from 6 to 7 grams/dl. The concentration is not critical, although as recognized by those skilled in the art the  
15 osmolarity of the solution should be compatible with the administration route (central or peripheral venous), and excessive water should not be given as carrier for the nutrients if elimination is perceived by the clinician to be a problem.

The enteral compositions are formulated particularly to provide  
20 the total nutritional requirements of the patient. Thus the Recommended Daily Dietary Allowances for water and fat soluble vitamins, and for minerals are provided in a typical daily dosage of amino acids (about 1 g protein/day/kg of patient body weight) and calories (about 20 kcal/day/kg).



The composition and methods of this invention will be more fully understood by reference to the subsequent examples.

### Example 1

This contemplated example illustrates the use of an embodiment of the invention in an enteral feeding mode.

5       A 50 year old, 60kg male with an exacerbation of hepatic failure due to acute cirrhosis of the liver from chronic alcohol ingestion, and with significant weight loss due to under-nutrition, exhibited protein intolerance, characterized in part by elevated serum ammonia values ( $>100\mu\text{g/dl}$ ). The patient had a history of episodes  
10 of coma.

The composition to be administered to this patient had the following approximate analysis:

|                           | G/96g<br>PACKET   | %(W/W) | KCAL/<br>PACKET | CALORIES<br>AS % TOTAL |
|---------------------------|---|--------|-----------------|------------------------|
| 15   L-Amino Acids        | 10.0  | 10.4   | 40              | 10.6                   |
| Carbohydrate <sup>†</sup> | 73.2  | 76.3   | 292.9           | 77.4                   |
| Fat*                      | 5.0   | 5.3    | 45.4            | 12.0                   |
| Total nitrogen:           | Approximately 1.55g/3.4 oz (96) packet  |        |                 |                        |
| Total calories:           | Approximately 378/3.4 oz (96 g) packet<br>(338 nonprotein calories)   |        |                 |                        |
| 20   Osmolarity:          | At the usual dilution of 1.1 kcal/ml,<br>the approximate osmolarity is 550 mOsm/l<br>(osmolality is 690 mOsm/kg water). |        |                 |                        |

\*Sunflower oil, medium chain triglycerides (fractionated coconut oil).

25   <sup>†</sup>Glucose oligosaccharides, sucrose.



The amino acid, vitamin and mineral constituents were as follows:

|    | <u>AMINO ACIDS</u>        | <u>AMOUNT (G) PER 3.4 OZ</u><br><u>(96 G) PACKET (378 KCAL)</u> |
|----|---------------------------|---|
| 5  | L-Leucine                 | 2.0   |
|    | L-Isoleucine              | 1.67  |
|    | L-Valine                  | 1.33  |
|    | L-Lysine-HCl (1.22g)      | free base 1.17  |
|    | L-Lysine-acetate (0.21 g) |   |
| 10 | L-Threonine               | 0.37  |
|    | L-Methionine              | 0.13  |
|    | L-Phenylalanine           | 0.10  |
|    | L-Tryptophan              | 0.10  |
|    | L-Arginine                | 1.17  |
| 15 | L-Proline                 | .73   |
|    | L-Alanine                 | .57   |
|    | Glycine                   | .33   |
|    | L-Histidine               | .33   |
| 20 | <u>VITAMINS/MINERALS</u>  |   |
|    | Vitamin A                 | 167 R.E.**  |
|    | Vitamin D                 | 33 I.U.   |
|    | Vitamin E                 | 1.7 T.E.**  |
| 20 | Vitamin C                 | 15 mg   |
|    | Folic Acid                | 67 mcg  |
|    | Vitamin B <sub>1</sub>    | 233 mcg   |
|    | Vitamin B <sub>2</sub>    | 267 mcg   |
|    | Niacin                    | 3 mg  |
| 25 | Vitamin B <sub>6</sub>    | 367 mcg   |
|    | Vitamin B <sub>12</sub>   | 0.5 mcg   |
|    | Biotin                    | 25 mcg  |
|    | Pantothenic Acid          | 0.9 mg  |
|    | Vitamin K <sub>1</sub>    | 17.5 mcg  |
| 30 | Choline                   | 67 mg   |
|    | Sodium                    | 153 mg  |
|    | Potassium                 | 392 mg  |
|    | Calcium                   | 133 mg  |
|    | Magnesium                 | 65 mg   |
| 35 | Phosphorus                | 165 mg  |
|    | Chloride                  | 237 mg  |
|    | Zinc                      | 2.5 mg  |
|    | Iodine                    | 25 mcg  |
|    | Manganese                 | 417 mcg   |
| 40 | Iron                      | 3.0 mg  |
|    | Copper                    | 333 mcg   |

\*\*R.E. = Retinol equivalents; T.E. = Tocopherol equivalents

The 96g packet of the above composition is mixed with 270ml  
45 of water to yield approximately 350ml.



The solution is administered via a nasogastric tube.

The composition was diluted to half strength and fed for two days, working up to a feeding rate of full strength of approximately 20 - 24 grams of protein/hour in a total fluid volume of approximately 2,000 milliliters/day. Feeding was continuous over each 24-hour period. The patient's serum ammonia values decreased to a greater degree than ordinarily would be expected when compared to a diet containing a greater amount of ammonotelic amino acids.

The patient resumed taking meals after one week of enteral feeding with the above composition, after which the composition was used occasionally for supplementary nutrition.



Example 2

This contemplated example illustrates the use of an embodiment of the invention in a parenteral feeding mode. A 50 year old, 55kg male with an acute exacerbation of hepatic failure due to cirrhosis of the liver secondary to chronic alcohol ingestion, and with significant weight loss due to under-nutrition, exhibited protein intolerance characterized in part by elevated serum ammonia (>100ug/dl). The patient had a history of encephalopathy and was unable to tolerate enteral feedings.

10 The parenteral amino acid composition to be administered contained the following:

|    |                 |                 | <u>mg/dl</u> |
|----|-----------------|-----------------|--------------|
|    | L-leucine       |                 | 1000         |
|    | L-isoleucine    |                 | 833          |
| 15 | L-valine        |                 | 667          |
|    | L-lysine        | (704) free base | 583          |
|    | L-methionine    |                 | 67           |
|    | L-phenylalanine |                 | 50           |
|    | L-threonine     |                 | 183          |
| 20 | L-tryptophan    |                 | 50           |
|    | L-histidine     |                 | 167          |
|    | L-arginine      |                 | 583          |
|    | L-proline       |                 | 367          |
|    | glycine         |                 | 167          |
| 25 | L-alanine       |                 | 283          |

In addition the solution contained 20mEq acetate and 11mEq of chloride per liter. The pH was about 6.0 (by adjustment with acetic acid). About 3mEq/l of sodium bisulfite was, added as a stabilizer. Concomitant administration of electrolytes and glucose for injection to provide approximately 40kcal/kg (1500ml of 50% Dextrose) completed the nutritional regimen. The rate of administration was 125ml/hour by central venous catheter. The duration of this support was 10 days.



We Claim:

1. A composition for administration to a patient having liver disease, comprising nonessential and essential amino acids including L-histidine, and wherein about from 8 to 16 mole % of the composition consists of L-serine, L-histidine, L-threonine, L-tryptophan, L-glutamine and glycine taken together.
2. The composition of claim 1 wherein the ratio of essential amino acids to nonessential amino acids by weight ranges about from 5:1 to 1:1.
3. The composition of claim 1 wherein the nonessential amino acids comprise greater than about 20% by weight of the total amino acids in the composition.
4. The composition of claim 1 wherein the mole % of L-serine, L-histidine, L-threonine, L-tryptophan, L-glutamine and glycine taken together ranges about from 10 to 15.
5. The composition of claim 4 wherein said mole % ranges about from 11 to 13.
6. The composition of claim 1 containing L-leucine, L-isoleucine and L-valine in a total of about 50% of the composition by weight.
7. The composition of claim 1 wherein the nonessential amino acids comprise about from 60 to 75% by weight of the total amino acids in the composition.
8. A composition for administration to a patient having liver disease, comprising a cysteine and serine-free mixture of essential and nonessential amino acids in the following proportions:



|    | <u>Amino Acids</u> | <u>Mole Percent<br/>about from</u> |
|----|--------------------|------------------------------------|
|    | L-Leucine          | 19.4 to 19.8                       |
|    | L-Isoleucine       | 16.2 to 16.4                       |
| 5  | L-Valine           | 14.5 to 14.8                       |
|    | L-Lysine           | 10.2 to 10.3                       |
|    | L-Methionine       | 1.1 to 1.2                         |
|    | L-Phenylalanine    | 0.7 to 0.9                         |
|    | L-Threonine        | 2.3 to 3.9                         |
| 10 | L-Tryptophan       | 0.5 to 0.7                         |
|    | L-Histidine        | 2.7 to 2.8                         |
|    | L-Arginine         | 8.5 to 8.7                         |
|    | L-Proline          | 8.1 to 8.3                         |
|    | Glycine            | 5.6 to 5.8                         |
| 15 | L-Alanine          | 8.1 to 8.3                         |

9. The composition of claim 8 wherein the mole percentages of L-leucine, of L-isoleucine, L-valine, L-lysine, L-methionine, L-phenylalanine, L-threonine, L-tryptophan, L-histidine, L-arginine, L-proline, glycine and L-alanine are, respectively, about 19.4, about 16.2, about 14.5, about 10.2, about 1.1, about 0.8, about 3.9, about 0.6, about 2.7, about 8.5, about 8.1, about 5.6, and about 8.1.

10. The composition of claim 9 further comprising vitamins, minerals, and digestively assimilable carbohydrates and fats.

11. The composition of claim 9 in aqueous solution at an amino acid concentration of about from 1 to 10 grams/dl.

12. A method for nutritional management of a patient with liver disease comprising enterally administering the composition of claims 9, 10, or 11 to the patient.

13. The composition of claim 8 wherein the mole percentages of L-leucine, L-isoleucine, L-valine, L-lysine, L-methionine, L-phenylalanine, L-threonine, L-tryptophan, L-histidine, L-arginine, L-proline, glycine and L-alanine are respectively about 19.8, about 16.4, about 14.8, about 10.3, about 1.2, about 0.8, about 2.3, about 0.6, about 2.8, about 8.7, about 8.3, about 5.8 and about 8.3.



14. The composition of claim 13 in sterile aqueous solution at a concentration of about from 3 to 10 grams of amino acid/dl.

15. The composition of claim 14 which is essentially free of electrolytes.

5 16. The composition of claim 9 comprising malate.

17. The composition of claim 14 comprising a sterilizing amount of sodium bisulfite.

18. A method for treating a patient having liver disease, comprising parenteral administration of the composition of claims  
10 14 or 15 to the patient.



# INTERNATIONAL SEARCH REPORT

International Application No **PCT/US/00742**

| <b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>3</sup><br>According to International Patent Classification (IPC) or to both National Classification and IPC<br><b>Int. Cl. A61K 31/40 and 31/195</b>   |  |                                     |  |  |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
|---|--|-------------------------------------|--|--|-------------------------------------|-------------|---|-----|---|--|-----|---|---|-----|---|---|-----|---|--|-----|-----|--|-----|
| <b>II. FIELDS SEARCHED</b><br><div style="text-align: right; font-size: small;">Minimum Documentation Searched <sup>4</sup></div> <table style="width: 100%; border: none;"> <tr> <td style="width: 25%; border: none; vertical-align: top;"> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%; font-size: small;">Classification System</th> <th style="width: 50%; font-size: small;">Classification Symbols</th> </tr> <tr> <td style="height: 40px; vertical-align: top; padding: 5px;"><b>U.S.</b></td> <td style="padding: 5px;"><b>424/274, 319</b></td> </tr> </table> </td> <td style="border: none;"></td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>5</sup></div>   |  |                                     | <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%; font-size: small;">Classification System</th> <th style="width: 50%; font-size: small;">Classification Symbols</th> </tr> <tr> <td style="height: 40px; vertical-align: top; padding: 5px;"><b>U.S.</b></td> <td style="padding: 5px;"><b>424/274, 319</b></td> </tr> </table>  | Classification System  | Classification Symbols              | <b>U.S.</b> | <b>424/274, 319</b>                                   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
| <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%; font-size: small;">Classification System</th> <th style="width: 50%; font-size: small;">Classification Symbols</th> </tr> <tr> <td style="height: 40px; vertical-align: top; padding: 5px;"><b>U.S.</b></td> <td style="padding: 5px;"><b>424/274, 319</b></td> </tr> </table>   | Classification System  | Classification Symbols              | <b>U.S.</b>  | <b>424/274, 319</b>  |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
| Classification System   | Classification Symbols   |                                     |  |  |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
| <b>U.S.</b>   | <b>424/274, 319</b>  |                                     |  |  |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
| <b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>14</sup> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; font-size: small;">Category <sup>6</sup></th> <th style="width: 70%; font-size: small;">Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup></th> <th style="width: 20%; font-size: small;">Relevant to Claim No. <sup>18</sup></th> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td>U.S., A, 3,832,465, Published 08 August 1974, Ghadimi</td> <td style="text-align: center; vertical-align: top;">all</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td>U.S., A, 3,950,529, Published 13 April 1976, Fischer et al</td> <td style="text-align: center; vertical-align: top;">all</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td>U.S., A, 4,025,650, Published 24 May 1977, Gans et al</td> <td style="text-align: center; vertical-align: top;">all</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td>U.S., A, 4,053,589, Published 11 October 1977, Gans et al</td> <td style="text-align: center; vertical-align: top;">all</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td>U.S., A, 4,259,353, Published 31 March 1981, Kleinberger</td> <td style="text-align: center; vertical-align: top;">all</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X,P</td> <td>U.S., A, 4,279,917, Published 21 July 1981, Takami et al</td> <td style="text-align: center; vertical-align: top;">all</td> </tr> </table> |  |                                     | Category <sup>6</sup>  | Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>   | Relevant to Claim No. <sup>18</sup> | X           | U.S., A, 3,832,465, Published 08 August 1974, Ghadimi | all | X | U.S., A, 3,950,529, Published 13 April 1976, Fischer et al | all | X | U.S., A, 4,025,650, Published 24 May 1977, Gans et al | all | X | U.S., A, 4,053,589, Published 11 October 1977, Gans et al | all | X | U.S., A, 4,259,353, Published 31 March 1981, Kleinberger | all | X,P | U.S., A, 4,279,917, Published 21 July 1981, Takami et al | all |
| Category <sup>6</sup>   | Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>   | Relevant to Claim No. <sup>18</sup> |  |  |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
| X   | U.S., A, 3,832,465, Published 08 August 1974, Ghadimi  | all                                 |  |  |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
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| X   | U.S., A, 4,025,650, Published 24 May 1977, Gans et al  | all                                 |  |  |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
| X   | U.S., A, 4,053,589, Published 11 October 1977, Gans et al  | all                                 |  |  |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
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| <div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;"> <p><b>* Special categories of cited documents: <sup>15</sup></b></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"G" document member of the same patent family</p> </div> </div>   |  |                                     |  |  |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
| <b>IV. CERTIFICATION</b> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> <div style="border-bottom: 1px solid black; margin-bottom: 5px;">Date of the Actual Completion of the International Search <sup>2</sup></div> <div style="text-align: center; font-weight: bold; margin-bottom: 5px;">15 SEP 1982</div> <div style="border-bottom: 1px solid black; margin-bottom: 5px;">International Searching Authority <sup>1</sup></div> <div style="text-align: center; font-weight: bold; font-size: 1.2em; margin-bottom: 5px;">ISA/US</div> </td> <td style="width: 50%; border: none; vertical-align: top;"> <div style="border-bottom: 1px solid black; margin-bottom: 5px;">Date of Mailing of this International Search Report <sup>2</sup></div> <div style="text-align: center; font-weight: bold; margin-bottom: 5px;">17 SEP 1982</div> <div style="border-bottom: 1px solid black; margin-bottom: 5px;">Signature of Authorized Officer</div> <div style="text-align: center; font-weight: bold; margin-bottom: 5px;">Primary Examiner</div> <div style="border-bottom: 1px solid black; margin-bottom: 5px;">[Signature]</div> </td> </tr> </table>   |  |                                     | <div style="border-bottom: 1px solid black; margin-bottom: 5px;">Date of the Actual Completion of the International Search <sup>2</sup></div> <div style="text-align: center; font-weight: bold; margin-bottom: 5px;">15 SEP 1982</div> <div style="border-bottom: 1px solid black; margin-bottom: 5px;">International Searching Authority <sup>1</sup></div> <div style="text-align: center; font-weight: bold; font-size: 1.2em; margin-bottom: 5px;">ISA/US</div> | <div style="border-bottom: 1px solid black; margin-bottom: 5px;">Date of Mailing of this International Search Report <sup>2</sup></div> <div style="text-align: center; font-weight: bold; margin-bottom: 5px;">17 SEP 1982</div> <div style="border-bottom: 1px solid black; margin-bottom: 5px;">Signature of Authorized Officer</div> <div style="text-align: center; font-weight: bold; margin-bottom: 5px;">Primary Examiner</div> <div style="border-bottom: 1px solid black; margin-bottom: 5px;">[Signature]</div> |                                     |             |   |     |   |  |     |   |   |     |   |   |     |   |  |     |     |  |     |
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